UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,745	12/21/2005	Jeffrey K. Kerns	PU60291	8275

20462 7590 08/23/2007

SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER	
BERNHARDT, EMILY B	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
08/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,745	KERNS ET AL.	
	Examiner	Art Unit	
	Emily Bernhardt	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7 and 9-11 is/are rejected.

7)☒ Claim(s) 8 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 12/21/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 1-7 and 9-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. "Hydroxylated derivatives" appearing in the R_5 definition is not clear as to what preceding group is being substituted with OH. Alkoxy? Aryl?

2. In claim 1 the choice for R5 as a bridging moiety recites "comprises" which is open-ended and thus includes more than what is positively recited. Also should not "alkyl" be "alkylene" in the definition ?

3. The scope of "Primary and Secondary conditions" in claim 10 is not fully ascertainable. While a list of diseases are given in the specification on p.2-3, it appears open-ended. Note the wording "include" which is open to diseases pertaining to other parts of the body in addition to those diseases mentioned which are directed towards the respiratory and the central nervous system. The terms are not otherwise art-recognized for a specific scope of diseases.

4. Structural makeup of rings formed at NR10R11 is not set forth in the claims nor in the specification as far as the examiner cand etermine. Note In re Wiggins 179 USPQ 421 regarding such terminology.

Claims 1-7 and 9-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following reasons apply.

Specification is not adequately enabled for scope of piperazines claimed which can have a variety of heterocycles including both fused and unfused, saturated and unsaturated as R2,R4 and R7-12. Compounds made and presumed tested (although actual test data is not seen) correspond to R2 as cycloalkyl with R4 being thiophene and for R8/R9 as a heterocycle only piperidino and pyrollidino is seen to have been made. There are no examples of NR10R11 rings. Furthermore the compounds can be fused on the quinoline ring with alkylene or dioxyalkylene chains. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to

structure-sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition, which includes factors such as:

1) Breadth of the claims- the claims cover compounds easily in the millions as pointed out above;

2) Level of unpredictability in the art- the invention is pharmaceutical in nature as it involves binding to neurokinin (NK-2, NK-3 or both) receptors. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See In re Fisher 166 USPQ 18. A range of IC50 values is reported which is huge- covering from 10nM to 1000nM for NK-3 antagonistic activity. Such a range is not informative as to what structural modifications will yield lead compounds for further testing. Note Ohnmacht cited by the examiner discusses a lead compound having a IC50 value of 11nM. See section on "NK2 ANTAGONISTS" on p.75;

3) Direction or guidance- as stated above the compounds made are not representative of the instant scope but are closer to each other than to remaining scope ;

4) State of the prior art- The compounds are piperazine derivatives substituted with various alkanoyl,carboxamido, carboalkoxy on one end and substituted with quinolinylalkyl on the other N terminus. While such compounds are known as evident from the art applied below, they are similar in structure to the compounds made herein and thus do not evidence the many structural permutations permitted in the instant scope are known for at least one use in the prior art;

5) Working examples- Actual test data has not been presented and thus no clear evaluation of which functional groups at various positions out of the many claimed might affect potency to a large or small degree.

In view of the above considerations, this rejection is being applied.

Claims 10-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There is no evidence that any piperazines instantly embraced have any one utility generically embraced in claim 10. Applicants have simply presented a huge list of disorders in the specification (pp.2-3) which applicants state can be

determined employing assays and **in vivo** tests relied on in various cited references. If it works I claim it is not compliance with 35 USC 112, par.one. In re Kirk 153 USPQ 48. The disclosed uses in this case are not only vast (see p.2-3 of the specification) but covers very difficult to treat diseases such as osteoarthritis, rheumatoid arthritis, Alzheimer's Disease, ALS, Down's Syndrome etc. No evidence is presented that instant compounds have such a myriad of capabilities. The Ohnmacht publication provided with this action emphasizes how preliminary the findings are regarding various NK receptors. See pages 75-76 which discusses some limited applications for NK-2 antagonists, namely coughing, bronchoconstriction while for NK-3 antagonsists, it is stated that studies of such have been limited. Also note Pattachini who discusses positive results for bronchoconstriction but not urinary tract disorders. See concluding sentence in section 3.1 on p.16. Also irritable bowel syndrome is linked with NK-2 anatagonists having undergone animal testing as discussed on p.18. With regard to Nk-3 antagonists, it is stated in the "Conclusions" section (on p.18) the following: "...but their role in human peripheral nervous system is much less documented". Furthermore, there is no evidence that any piperazines instantly embraced have the ability to treat whole classes of

respiratory diseases covered by claim 11. The scope is vast including diseases pertaining to humans as well as other animals such as HIV- and FeLV-associated respiratory illness as well as lung diseases of unknown cause. No evidence is presented that instant compounds have such a myriad of capabilities. The Ohnmacht publication provided with this action emphasizes how preliminary the findings are regarding various NK receptors. See pages 75-76 which discusses some limited applications for NK-2 antagonists, namely coughing, bronchoconstriction while for NK-3 antagonsists, it is stated that studies of such have been limited. Also note Pattachini who discussed positive results for bronchoconstriction . See concluding sentence in section 3.1 on p.16. With regard to Nk-3 antagonists, it is stated in the "Conclusions" section (on p.18) the following: "...but their role in human peripheral nervous system is much less documented".

Thus work in this area is only in the preliminary stages and such uses are not considered all treatable **much less preventable** based simply on having NK-2 and/or NK-3 receptor binding antagonistic activity. Where the utility is unusual or difficult to treat or speculative, the examiner has

authority to require evidence that tests relied on are reasonably predictive of *in vivo* efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Note MPEP. 2164.05(a) .

Note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition, which includes factors such as:

1) Level of unpredictability in the art- see discussion in the above par.one rejection for compounds;

2) Direction or guidance- The amount of guidance presented in the specification as to which compounds are sufficiently active to be useful for the claimed uses is nonexistent. The dosage range information (on p.15) is virtually useless being a 50 fold range and not directed to a specific disease;

3) Working examples- No test data has been presented only mention of assaya for assessing therapeutic potential. Also See Ex parte Stevens 16 USPQ 2d 1379 regarding sole reliance on description of testing protocol.

In view of the above considerations, this rejection is being applied.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3,5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Farina (WO'664). The commonly assigned WO publication has a publication date which precedes applicants' earliest foreign priority date. It describes a compound within the instant scope which is used as reactant. See description 13 on p.38. Note that claims 5-7 are also rejected since they do not exclude said compound from these claims but only narrow at other "R" choices.

Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

E Bernhardt

Emily Bernhardt
Primary Examiner
Art Unit 1624